Parameters estimation approach for the MEA/hiPSC-CM assays

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1) Motivation and goals

Human induced pluripotent stem cell-derived cardiomyocytes (**hIPSC-CMs**) are a promising tool in regenerative medicine (repair damaged areas) because of pluripotency and ability to differentiate [1]. Computational modeling and simulation is a powerful tool to investigate [2]:

- **drug effects** and their side effects
- **disease** in cardiac electrophysiological activity.

Our goal is to perform *in silico simulations* (quantify and predict affinities and effects of drugs on hIPSC-CMs) to be used in early stage of the development of new compounds. Here we provide an approach allowing to fit the drug model parameters to the experimental data.

2) Tissue model

Modeling a layer of hIPSC-CMs: **bidomain model** (terms in blue) solved in the 2D computational domain Ω of Fig. 1, to compute the membrane potential V_M and the extracellular potential u_e.

$$\begin{cases} \dfrac{d\mathbf{w}}{dt} - \mathbf{g}(V_M, \mathbf{w}) = 0 \text{ in } \Omega \\ A_M\left(C_M\dfrac{\partial V_M}{\partial t} + I_{ion}\right) - \text{div}\,(\sigma_I \nabla V_M) - \text{div}\,(\sigma_E \nabla u_e) = A_M I_{stim} \text{ in } \Omega \\ -\text{div}\,((\sigma_I+\sigma_E)\nabla u_e) - \text{div}\,(\sigma_I \nabla V_M) = \dfrac{1}{z_{thick}}\Sigma_{e_k}\dfrac{I^k_{el}}{|e_k|}\chi_{e_k} \text{ in } \Omega \end{cases} \quad (1)$$

- Ionic current I_{ion} computed with:
  - model proposed by Paci et al. [3] in the case of *pacemaker cells*
  - modified Paci model (with adult version of I_{Na}) in the case of *non-pacemaker cells*.
- Source term added to model a 60-6well MicroElectrode Array **MEA** (terms in red): device used to measure the *field potential* generated from multiple cells. The electrodes are described using the circuit in Fig. 1, by computing the measured current I^k_{el}:

$$\frac{dI^k_{el}}{dt} + \frac{I^k_{el}}{\tau} = \frac{C_{el}}{\tau}\frac{dU^k}{dt} \qquad \text{with } U^k = \frac{1}{|e_k|}\int_{e_k} u_e, \text{ for } k = 0,..,8, \quad (2)$$

where $\tau = (R_i + R_{el})C_{el}$, R_i is the inner resistance, R_{el} and C_{el} are the resistance and the capacitance of the electrode. The measured **field potential** is then $U^k_{mes} = R_i I^k_{el}$.

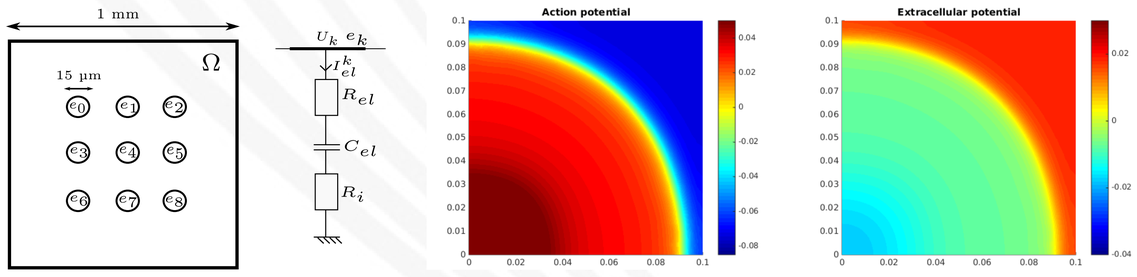


Figure 1: Left: domain Ω for the MEA model and equivalent circuit for the electrodes. Right: propagation of the depolarization front in the case of non-pacemaker cells stimulated in the left-bottom corner.

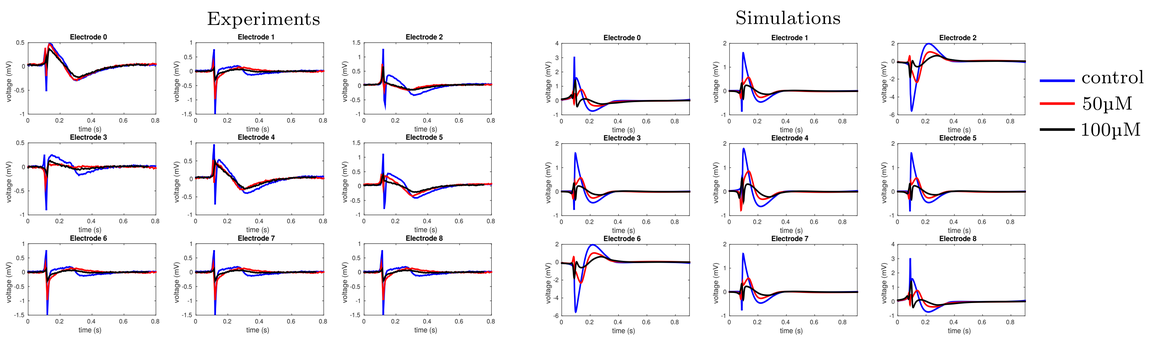
3) Drug action: Mexiletine example

Pore block model: use of a *conductance-block formulation* [2]. In the ionic model, the conductance of a targeted channel s is reduced by a scaling factor:

$$g_{blocked,s} = g_{control,s}\left[1 + \left(\frac{[D]}{IC_{50}}\right)^n\right]^{-1} \qquad \text{with } n = 1,$$

where $[D]$ is the drug concentration and the IC_{50} value is the dose able to block 50% of the channel activity.

- **Mexiletine**: action on I_{Na} (smaller depolarization phase)



4) Parameters estimation: drug dose $[D]$ example

- From given synthetical field potential measurements U^k_{mes} where a drug is blocking one ionic channel, **find the dose** $[D]_{mes}$ **which allowed to obtain these data**, knowing the concerned drug and its targeted channel.
- Define a **cost function** $J([D])$ minimizing the distance between the simulated and the synthetical field potential measurements:

$$J([D]) = \tfrac{1}{2}\Sigma_{e_k} \parallel R_i I^k_{el}([D]) - U^k_{mes} \parallel^2_{l^2([0,T])} \quad (3)$$

where $I^k_{el}([D])$ is solution of the tissue model ((1) + (2)). Our goal is to find $[D]$ minimizing (3).

- For this, define an **adjoint problem** associated to the tissue model:

$$\begin{cases} -\dfrac{d\mathbf{q}}{dt} + {}^t(\partial_{\mathbf{w}}\mathbf{g}(V_M,\mathbf{w},[D]))\mathbf{q} - A_M{}^t(\partial_{\mathbf{w}} I_{ion}(V_M,\mathbf{w},[D]))p_M = 0 \text{ in } \Omega \\ A_M\left(C_M\dfrac{\partial p_M}{\partial t} - \partial_{V_M} I_{ion}(V_M,\mathbf{w},[D])\right)p_M + \text{div}\,(\sigma_I\nabla p_M) \\ \qquad + \text{div}\,(\sigma_I\nabla p_e) + {}^t(\partial_{V_M}\mathbf{g}(V_M,\mathbf{w},[D]))\mathbf{q} = 0 \text{ in } \Omega \\ \text{div}\,((\sigma_I+\sigma_E)\nabla p_e) + \text{div}\,(\sigma_I\nabla p_M) = \Sigma_{e_k}\dfrac{C_{el}}{\tau}\dfrac{1}{|e_k|}\dfrac{d\lambda^k}{dt}\chi_{e_k} \text{ in } \Omega \\ \dfrac{d\lambda^k}{dt} - \dfrac{\lambda^k}{\tau} = -\dfrac{1}{z_{thick}}P^k_e - R_i(R_i I^k_{el} - U^k_m) \text{ in } e_k, \text{ for } k = 0,..,8 \end{cases} \quad (4)$$

with $P^k_e = \frac{1}{|e_k|}\int_{e_k} p_e$ and with $\mathbf{q}$, p_M, p_e and λ^k states adjoint associated respectively to states $\mathbf{w}$, V_M, u_e and I^k_{el} and solution of (4).

- The **cost function gradient** is given by:

$$\partial_{[D]}J([D]) = \int_\Omega\int_0^T {}^t(\partial_{[D]}\mathbf{g}(V_M,\mathbf{w},[D]))\mathbf{q} - \int_\Omega\int_0^T A_M\partial_{[D]}I_{ion}(V_M,\mathbf{w},[D])p_M \quad (5)$$

- We use an optimization procedure based and gradient descent method.

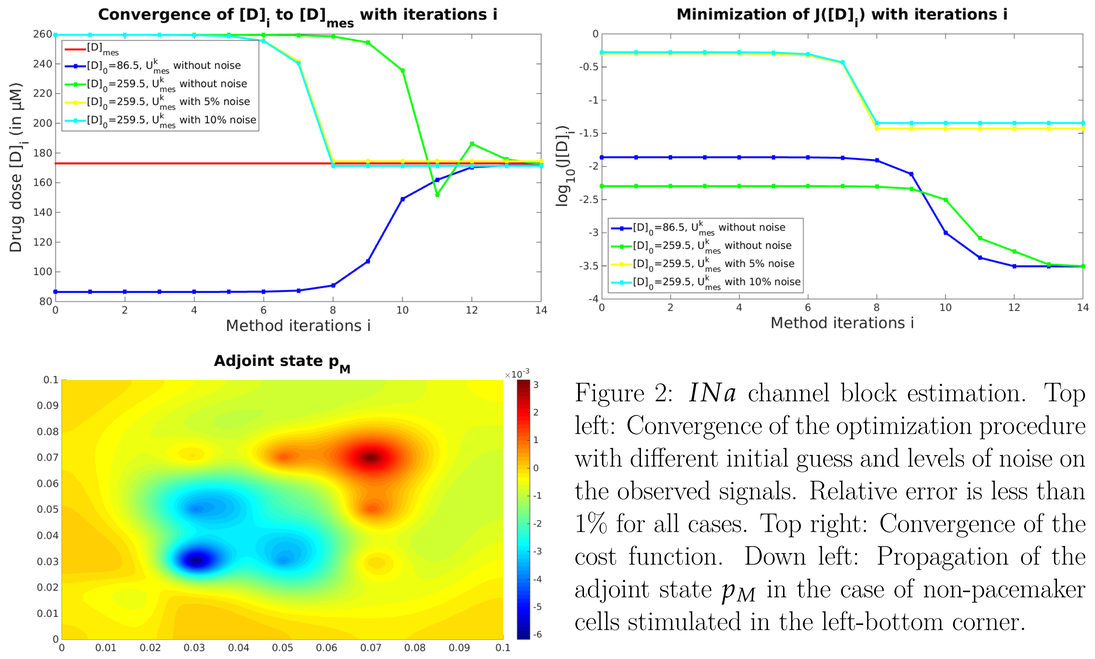


Figure 2: *INa* channel block estimation. Top left: Convergence of the optimization procedure with different initial guess and levels of noise on the observed signals. Relative error is less than 1% for all cases. Top right: Convergence of the cost function. Down left: Propagation of the adjoint state p_M in the case of non-pacemaker cells stimulated in the left-bottom corner.

5) Discussion and future work

We presented a proof of concept of an optimization approach able to estimate the drug dose of a compound when the characteristics of the drug are known. The robustness of the method was tested on drugs targeting *INa* channel using in silico experiments: with 10 % of gaussian noise on the observed field potential, the accuracy of the estimated drug dose is higher than 99%. Future developments would include estimating model parameters of drugs like Mexelitine or Dofetilide, drugs with several targeted channels and fitting of other parameters as IC_{50}, etc.

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